Psychology & Neuroscience
ISSN: 1984-3054
landeira@puc-rio.br
Pontifícia Universidade Católica do Rio de Janeiro
Brasil

Machinskaya, Regina I.; Semenova, Olga A.; Absatova, Ksenya A.; Sugrobova, Galina A.
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Psychology & Neuroscience, vol. 7, núm. 4, 2014, pp. 461-473
Pontifícia Universidade Católica do Rio de Janeiro
Rio de Janeiro, Brasil

PSYCHOLOGY & NEUROSCIENCE

Psychology & Neuroscience, 2014, 7, 4, 461-473
DOI: 10.3922/j.psns.2014.4.05

Neurophysiological factors associated with cognitive deficits in children with ADHD symptoms: EEG and neuropsychological analysis

Regina I. Machinskaya[1], Olga A. Semenova[1], Ksenya A. Absatova[1], and Galina A. Sugrobova[2]

1- Russian Academy of Education, Moscow, Russia

2- Penza State University, Penza, Russia

Abstract

We neuropsychologically assessed cognitive deficits in 109 children with symptoms of attention-deficit/hyperactivity disorder (ADHD) and 51 children with typical development aged 7-8 years and 9-10 years and visually analyzed resting-state electroencephalography (EEG). The EEG recordings of children with ADHD more frequently contained EEG patterns of fronto-thalamic non-optimal functioning compared with controls, reflected by groups of bilaterally synchronous frontal theta waves (FTWs) and right hemisphere local deviations of brain electrical activity. We found cognitive impairments associated with ADHD in children with different deviations of resting-state EEG. Children with FTWs in both age groups exhibited pronounced difficulties in programming, regulation and control (executive functions), and verbal performance. Children with right hemisphere local EEG abnormalities had executive dysfunction combined with difficulties in nonverbal performance. Executive performance in typically developing children significantly improved from 7-8 to 9-10 years of age. An analysis of neuropsychological scores in children with ADHD symptoms from age 7-8 to 9-10 with the same EEG abnormalities indicated specific age-related improvement of cognitive abilities. In children whose EEG showed patterns of fronto-thalamic involvement presented significant improvement in executive and verbal performance from 7-8 to 9-10 years of age. Overcoming the same age gap in children with right hemisphere local EEG deviations significantly improved only nonverbal performance, whereas improvements in executive function were not statistically significant. **Keywords:** attention-deficit/hyperactivity disorder, cognitive deficits, fronto-thalamic system, right hemisphere, neuropsychology, EEG, primary schoolchildren.

Received 19 June 2014; received in revised form 11 November 2014; accepted 12 November. Available online 16 December 2014.

Introduction

Most children with attention-deficit/hyperactivity disorder (ADHD) and impulsiveness face learning difficulties (Zavadenko & Petroukhin, 2007; Loe & Feldman, 2007). Approximately 70-80% of ADHD children have poor academic performance (Barkley, 2006; Daley & Birchwood, 2010; Corkum, McGonnell, & Schachar, 2010). Daley and Birchwood (2010) showed that learning difficulties in ADHD children were more likely to arise from cognitive deficits than classroom misbehavior. Many neurocognitive studies (Barkley, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; for review, see Solovieva, Machinskaya, Bonilla, & Quintanar, 2007) have reported that executive dysfunction (i.e., poor inhibitory control, poor planning, and difficulty following instructions) is the main cognitive deficit in ADHD children. Moreover, ADHD symptoms can be caused by inappropriate motivation, manifested by delay aversion (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008) and low energy levels (Sergeant, 2005). Together with executive dysfunction, ADHD subjects exhibit modality-dependent cognitive deficits such as language and visuospatial impairments. ADHD children exhibit low verbal (Pineda, Restrepo, Henao, Gutierrez-Clellen, & Sanchez, 1999) and nonverbal (Nijokiktjien & Verschoor, 1998) Intelligence Quotient scores, low verbal memory performance, poor inner speech, difficulty in concept formation (Zavadenko & Petroukhin, 2007), poor visuospatial skills (Quintanar, Solovieva, & Bonilla, 2006), and poor categorical reasoning in both visual and verbal tasks (Machinskaya & Semenova, 2004). Such a wide range of cognitive deficits is thought to be caused by the heterogeneity of ADHD, which was observed and verified by many studies. ADHD symptoms (DuPaul, 1998) have different etiologies and are associated with dysfunctions in

Regina I. Machinskaya, Olga A. Semenova, and Ksenya A. Absatova, Laboratory of Neurophysiology of Cognitive Processes, Institute of Developmental Physiology, Russian Academy of Education. Galina A. Sugrobova, Biology Department, Penza State University. Correspondence regarding this article should be directed to: Regina Machinskaya, Laboratory of Neurophysiology of Cognitive Processes, Institute of Developmental Physiology, Russian Academy of Education, Pogodinskaya str. 8-2, Moscow, 119869, Russia. E-mail: reginamachinskaya@gmail.com

different brain systems (Dickstein, Bannon, Castellanos, & Milham, 2006; Castellanos & Proal, 2012).

The most popular model of the brain mechanisms of ADHD is the prefronto-striatal model (Krain & Castellanos, 2006). This model explains ADHD symptoms through inhibitory control deficits associated with morpho-functional changes in the prefrontal cortex and striatopallidal system composed of the dorsal striatum, dorsal pallidum, ventral striatum, and ventral pallidum. However, striatopallidal dysfunction alone cannot explain all of the varieties of cognitive deficits mentioned above. In fact, many functional neuroimaging studies have shown lower activation of neural networks across different brain regions in ADHD children and adolescents compared with controls both during cognitive tasks and in a resting state (Dickstein et al., 2006; Castellanos & Proal, 2012). A meta-analysis (Dickstein et al., 2006) reported lower activation in the left prefrontal cortex (Brodmann areas [BA] 6, 8, 13, and 44), anterior cingulate cortex (BA 24 and 32), temporal regions (bilaterally BA 7 and 40 in the right hemisphere), right-hemisphere thalamus and striatum, and left occipital area (BA 19) during selective attention tasks in ADHD patients. Various morpho-functional brain changes were also found in studies of resting state networks in ADHD subjects (Yeo et al., 2011). A decrease in the functional connectivity between prefrontal, temporal, and occipital cortices and other regions was observed in ADHD adults and children (Wang et al., 2009). Based on functional magnetic resonance imaging (fMRI) results (Castellanos & Proal, 2012), ADHD symptoms may be explained by a decrease in functional integration across brain structures, including different resting-state networks (e.g., fronto-parietal control network, dorsal network involved in selective attention, movement control network, visual network, and default network).

Electroencephalographic (EEG) studies have shown that abnormal electrical activity in the brain in ADHD subjects may be associated with the non-optimal functioning of different brain systems that are responsible for information processing and executive control (Banaschewski & Brandeis, 2007; Loo & Makeig, 2012). The first EEG data on behavioral problems in children were collected at the dawn of electrophysiology in which slow 5-6 Hz waves were recorded from frontal leads (Jasper, Solomon, & Bradley, 1938). Later, qualitative EEG studies corroborated the presence of slow theta waves in the frontal and central cortices in ADHD subjects (Chabot & Serfontein, 1996; Lazzaro et al., 1998; Bresnahan & Barry, 2002; Hermens, Soei, Clarke, Kohn, Gordon, & Williams, 2005; Williams et al., 2010) and provided another argument in favor of the frontal lobe origin of ADHD. However, the analysis of EEG data that were collected from ADHD children with different sets of behavioral symptoms (inattentive/hyperactive-impulsive/combined types) suggested that frontal theta waves were specific only to the inattentive type (Lubar Swartwood, Swartwood, & Timmermann, 1995; Machinskaya & Krupskaya, 2001; Barry, Clarke, & Johnstone, 2003). The predominantly hyperactive-impulsive type of ADHD was associated with slow waves not in frontal regions but rather in caudal (occipital and parietal) regions (Matousek, Rasmussen, & Gilberg, 1984; Barry et al., 2003), which was explained as a pattern of low brain cortical activation and/or central nervous system immaturity. In addition to these deviations, the combined type of ADHD could also involve another abnormality such as an increase in frontal beta oscillations (Chabot & Serfontein 1996; Clark, Barry, McCarthy, & Selikowitz 2001; Arns, Gunkelman, Breteler, & Spronk, 2008).

Thus, cognitive and behavioral deficits associated with ADHD involve different brain impairments and, hence, should be studied in an interdisciplinary manner to perform adequate differentiation analyses and support children with learning difficulties. Special attention should be paid to neurophysiological studies of primary schoolchildren because most of their cognitive and behavioral difficulties are manifested at the beginning of school learning.

In the current study, we applied Luria's approach of the dynamic localization of higher mental functions (Luria, 1973) to study brain mechanisms associated with learning difficulties with regard to functional brain systems. In addition to the notion of the multiplicity of neural networks involved in cognitive performance, A.R. Luria was the first to treat the components of higher mental functions and their corresponding brain activity as different levels of the same phenomenon (i.e., human cognitive activity). Classifying brain structures according to the main components of cognitive activity was realized in the theory of three functional units. By analyzing cognitive performance in patients with different local brain injuries, Luria described three functional brain units: I (arousal unit), II (information processing and storage unit), III (programming, regulation, and control unit). The first and third units provide cognitive regulation and can be defined as *regulatory* components, whereas the second unit can be defined as the *information-related* component. Luria also studied cognitive activity in brain-damaged patients to differentiate separate structures within each functional unit. Today, modern neuroscience has many noninvasive methods for studying brain mechanisms associated with cognitive performance in both patients and healthy subjects, and much experimental confirmation has been provided for Luria's theory. Despite the fact that Luria's concept derived from the study of brain injury, it is also applied for the assessment and remediation of children with learning difficulties, including ADHD (Quintanar, Hernández, Bonilla, Sánchez, & Solovieva, 2001; Akhutina & Pilayeva, 2012).

In terms of Luria's theory, learning difficulties are caused by *weakened* components of mental functions associated with the poor activation or immaturity of a certain functional brain system. These changes in the brain are considered neurophysiological factors

associated with cognitive deficits. Particular cognitive deficits (e.g., executive control deficits) can have the same neurophysiological factors, regardless of the nosological form of learning difficulties. Therefore, we can define the search for the brain mechanisms that underlie learning difficulties as the search of the neurophysiological factors associated with cognitive deficits. This goal can be achieved through the following steps: (1) neuropsychological assessment of cognitive abilities associated with regulatory and information-related components in children with learning difficulties to detect *weak* links, (2) neurophysiological assessment of brain activity associated with regulatory and information-related components, and (3) determining correlations between *weakened* cognitive operations and the dysfunction of specific brain systems.

Within the framework of neurophysiological studies of the mechanisms that underlie cognitive deficits in children, a variant of qualitative EEG analysis (Machinskaya, Lukashevich, & Fishman, 1997; Lukashevich, Machinskaya, & Fishman, 1999) was developed based on Luria's concept of brain functional units. This analysis, referred to as *structural EEG analysis*, aims to help an expert describe abnormal patterns of a resting-state EEG and associate them with neuropsychological measures of cognitive deficits.

Despite the absence of a definitive connection between EEGs and a particular disease (i.e., EEG nosological nonspecificity), many clinical studies have reported robust correlations between the specific shape and topography of abnormal EEG patterns and pathological or functional changes in brain structures (Hughes, 1994; Niedermeyer & Lopes da Silva, 2005). In clinical case studies, a common practice is to extract such unusual patterns from the resting-state EEG and test whether they are predictive of abnormal brain conditions. The detection of such patterns is usually performed via visual inspection of the EEG by a clinical expert. Far less frequently, the expert assessment of an EEG is used in group studies. This is partly due to the absence of objective methods for pattern detection and partly due to disbelief in qualitative expert assessment. However, despite the obvious lack of objectivity, a visual analysis nonetheless has an important advantage: the expert can detect and identify fast-changing EEG patterns. Because of the transient nature of these patterns and complexity of their waveforms, devising a strict computational detection method is difficult.

In the *structural EEG analysis*, the various abnormal patterns are classified according to their associations with the state of function of different brain structures. Certain classes relate a group of patterns to the state of function of the cortex as a whole (main alpha rhythm characteristic and diffused nonlocalized EEG abnormalities), different cortical areas (focal intrahemispheric EEG abnormalities), or deep regulatory structures (bilaterally synchronous EEG abnormalities). The classification of abnormal EEG patterns is based on expert judgments and clinical EEG data. The structural EEG analysis provides sufficiently detailed information about the state of function of different brain structures, thus making it easier to relate the EEG data to the data obtained from other sources (e.g., neuropsychological scores). In particular, this approach allows one to uncover correlations between neuropsychological scores that reflect deficits in regulatory and information components of cognitive processing and EEG patterns that reflect non-optimal states of function of deep brain structures, specific cortical areas, and the cortex as a whole.

Structural EEG analysis helped identify three abnormal EEG patterns that are typical in ADHD preschool and primary school children compared with controls (Machinskaya & Krupskaya, 2001; Solovieva et al., 2007; Sugrobova, Semenova, & Machinskaya, 2010). The first and most frequently observed abnormal EEG pattern consists of bilaterally synchronous frontal theta waves (FTWs; Figure 1, I). Clinical EEG studies (Mayorchik, 1973; Lukashevich & Sazonova, 1996; Hughes, 1994) and neurophysiological experiments (Kim et al., 2011) showed that FTWs reflect the abnormal activity of neuronal networks in the thalamic mediodorsal nucleus (MD) and/or prefrontal cortex, together comprising the *fronto-thalamic system* (Goldman-Rakic & Porrino 1985; Zhang, Snyder, Shimony, Fox, & Raichle, 2010). The albeit rather indirect reasons for the thalamo-cortical origin of bilaterally synchronous FTWs are discussed in our previous paper (Kurgansky & Machinskaya, 2012). The quantitative analysis of FTW patterns performed in that study showed that the appearance of bilaterally synchronous waves were accompanied by a strengthening of the statistical association among the group of sensors that showed the most theta waves and a simultaneous reduction of the strength of functional connectivity between these and other sensors. A comparison of morphological, clinical, and neurophysiological data led to the suggestion that such partial "autonomization" of the group of frontal and central sensors is due to thalamo-cortical interactions.

The fronto-thalamic regulatory system plays an important role in the selective modulation of cortical activity during voluntary attention (Machinskaya, 2006) and working memory performance (Watanabe & Funahashi, 2012). Hereinafter, we use *fronto-thalamic non-optimal functioning* to describe brain activity changes involved in FTWs because the EEG method lacks precise information about deviations in neuronal activity in networks between the prefrontal cortex and MD. The comparison of EEG parameters in groups of children aged 5-6 years, 6-7 years, and 7-8 years (Machinskaia, 1997) led to the assumption that FTWs that are found in 6- to 8-year-old children could result from fronto-thalamic immaturity. The presence of FTWs in ADHD adults (Loo & Barkley, 2005) and patients with thalamic lesions (Lukashevich & Sazonova, 1996; Hughes, 1994) favors the notion that FTWs result from dysfunction or injury of the fronto-thalamic system.

Groups of slow bilaterally synchronous waves recorded from caudal (occipital and parietal) brain areas

and/or hypersynchronous high-amplitude alpha rhythms (> 120 μV) is the second EEG pattern (Figure 1, II) that distinguishes ADHD children from their typically developing peers. This pattern is associated with low cortical excitability (Steriade, 2000) and related to a decrease in activity of the brainstem reticular formation (Omata, Hanakawa, Morimoto, & Honda, 2013). Thus, hypersynchronous high-amplitude alpha and theta oscillations can be considered EEG signs of deficits in nonspecific cortical activation. These EEG changes can be related to the first unit in Luria's scheme and thus reflect regulatory process deficits. The third EEG pattern that is typical in ADHD children is local deviations in electrical activity of the right hemisphere. This pattern consists of sharp theta waves (Figure 1, III). The third pattern cannot be attributed exclusively to deficits in either regulatory or information-related processes because clinical (Myers, 1999) and neurocognitive (Posner & Petersen, 1990; Tanaka, 1996) data show that large-scale networks in the right hemisphere subserve regulatory processes (e.g., fronto-parietal attention system) and are also involved in information processing (e.g., a known role for the right inferior temporal cortex in object recognition). Importantly, ADHD children can have one of the aforementioned EEG patterns or different combinations.

Despite the large number of ADHD studies, still unresolved is the possible trajectory of cognitive development that is specific to ADHD children. When attempting to clarify this issue, one may encounter much contradictory data. According to Brodeur and Pond (2001), voluntary attention in ADHD children has the same developmental trajectory from ages 6-8 years to 9-11 years, as in typically developing children, despite lower attention scores in ADHD children of both ages. Another study (Gupta & Kar, 2009) found no progressive changes in most of the cognitive parameters in children from 6 to 9 years of age. These contradictions and the variety of cognitive deficits could be caused by the heterogeneity of brain mechanisms associated with ADHD.

To uncover the neurophysiological factors associated with learning difficulties in ADHD children, we tested whether different profiles of cognitive deficits and/or different trajectories of cognitive development are related to the following abnormal EEG patterns: FTWs, local deviations in electrical activity of the right hemisphere, and hypersynchronous alpha/theta oscillations in caudal regions.

Methods

Participants

The study was conducted at the Diagnostic Center of the Institute of Developmental Physiology, Russian Academy of Education. All of the children who volunteered to assist us in the study attended regular classes in mainstream schools in Moscow and had no history of neurological or psychiatric illness. Their parents provided written informed consent.

A total of 362 children, 7-10 years of age, underwent a behavioral assessment of ADHD symptoms, resting-state EEG analysis of brain function, and a detailed cognitive assessment.

For the behavioral assessment, we applied the ADHD Rating Scale-IV (DuPaul, 1998), which includes a list of 18 behavioral symptoms of ADHD (nine symptoms describe inattentiveness and nine describe hyperactivity/impulsiveness) based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. We chose this questionnaire because it is simple to complete and score, and it is one of the most frequently applied screening tools. A questionnaire was completed by teachers and/or parents. Following the criteria suggested in DuPaul (1998), we considered a child as having ADHD when (*i*) the child was rated with six or more inattentive symptoms and more than one but less than six hyperactivity/impulsiveness symptoms (i.e., inattentive subtype), (*ii*) the child was rated with six or more hyperactivity/impulsiveness symptoms and more than one but less than six inattentive symptoms (i.e., hyperactive/impulsive subtype), and (*iii*) the ratings were equal to or greater than six for both scales (i.e., combined subtype). For further analysis, all of the ADHD children were pooled into a single ADHD sample because searching for subtype-specific EEG correlates was outside the scope of the present work.

According to these scores, we formed main groups with ADHD symptoms and control groups aged 7-8 years and 9-10 years (Table 1). Moreover, the control groups had another selection criterion, namely, good academic performance (i.e., no learning difficulties).

Materials and procedure

The cognitive assessment was performed using Luria's neuropsychological battery that was adapted for primary school children (Akhutina, Ignatieva, & Maksimenko, 1996) and included 23 tests. For each child, after completing each test, we scored several parameters associated with different components of cognitive performance. The total score was computed over different tests for each cognitive component and reflected the absence/presence of deficits (Table 2). We then computed integral neuropsychological indices, which showed the degree of executive dysfunction, impairment of verbal and non-verbal functions, and energy deficits. The integral neuropsychological index is the ratio of the number of poor cognitive components included in a particular block (N_{poor}) to the total number of components in the same block (N_{total}). For example, if a child was rated with three poor cognitive components included in the *executive* block that consisted of seven components, then the child's integral neuropsychological index was .43 (3/7). The statistical analysis of neuropsychological parameters was performed using the Mann-Whitney U test for independent samples.

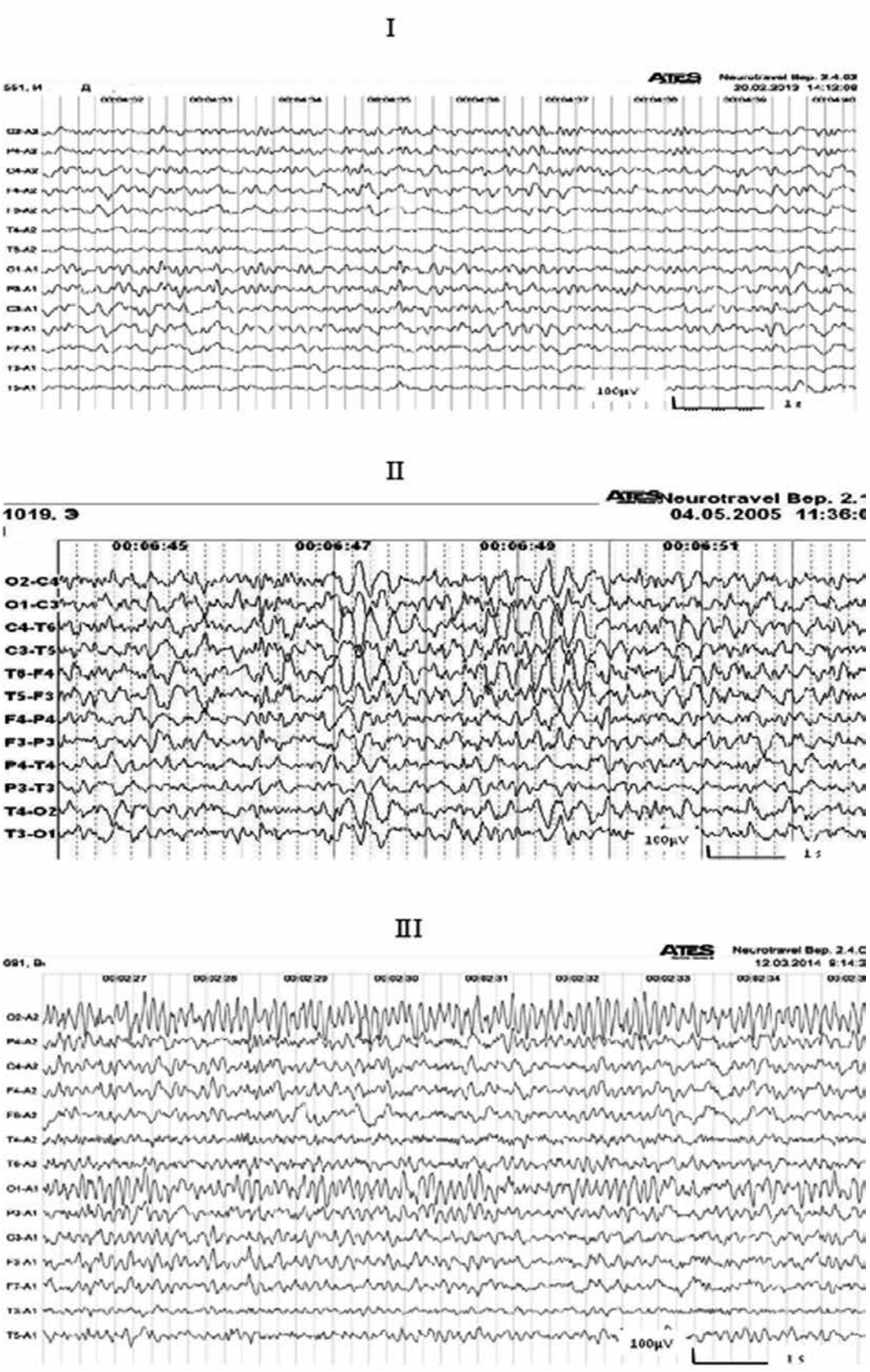

Figure 1. (I) Groups of bilaterally synchronous frontal theta waves (FTWs) in the frontal leads (*F4, F3*). The EEG pattern of non-optimal fronto-thalamic system functioning is shown for an 8-year-old boy. (II) Single sharp theta waves and groups of sharp theta waves show phase reversal at the right frontal lead (*F4*) and posterior temporal lead (*T6*), identified as local EEG changes in the right hemisphere (RH). The EEG fragment is shown for a 7-year-old girl with bipolar recording. (III) Hypersynchronous (> 120 mV) alpha rhythm in the occipital leads (*O1*, *O2*). EEG patterns associated with a deficit of nonspecific cortical activation (DA) are shown for a 7-year-old boy. The distance between the vertical lines is 200 ms in all EEG fragments. Figures in the bottom right corners show the 100 μV amplitude (vertical line) and 1 s duration (horizontal line) of the EEG signals.

Table 1. Distribution of children according to the presence of ADHD symptoms, age, and sex.

Group	7-8 years old			9-10 years old		
	Boys	**Girls**	**Number of subjects (mean age ± SD)**	**Boys**	**Girls**	**Number of subjects (mean age ± SD)**
Control	11	16	*n* = 27 8.16 ± .47 years	6	18	*n* = 24 9.96 ± .71 years
ADHD	42	8	*n* = 50 7.82 ± .56 years	48	11	*n* = 59 9.78 ± .67 years
Total	53	24	*n* = 61	54	29	*n* = 39

Table 2. Cognitive parameters analyzed during the neuropsychological assessment.

Integral neuropsychological indices ($I = N_{poor} / N_{total}$)	**Deviations of different cognitive components**
Executive dysfunctions	Difficulty following instructions Poor planning Impulsiveness Difficulty switching between program units within a task Difficulty in task switching Difficulty staying focused on a task Poor error monitoring
Verbal impairments	Poor articulation Deficit in processing speech sounds Poor phonemic awareness Verbal paraphasia Poor vocabulary skills Agrammatical speech
Non-verbal impairments	Poor kinesthetic sensitivity Poor tactile sensitivity Inability to integrate visual elements into a whole Poor spatial arrangement Difficulty coordinating picture details in two-dimensional space Poor visuospatial memory
Low energy level	Fatigue Poor arousal Slowness

The EEG was recorded under resting conditions with the eyes closed using 12 symmetrical leads: frontal (F3, F4), central (C3, C4), temporal (T3, T4), parietal (P3, P4), inferior temporal (T5, T6), and occipital (O1, O2), placed according to the international 10-20 system in monopolar (with ipsilateral ears electrodes) and bipolar montages. EEG was recorded using a Neurotravel 24 D COM computer electroencephalograph (ATESMEDICA, Russia) in the 1-70 Hz frequency band.

Each recording was visually analyzed by an expert and checked for three EEG patterns: bilaterally synchronous FTWs (Figure 1, I), right hemisphere local deviations (Figure 1, III), and hypersynchronous alpha rhythm and/or groups of theta oscillations in caudal divisions (Figure 1, II). The statistical analysis of group differences in the frequency of deviating EEG patterns was performed using Fisher's Exact Probability Test for 2 × 2 contingency tables.

Results

Influence of ADHD symptoms and age on cognitive activity in 7-8- and 9-10-year-old children

The ADHD and control groups differed in sex ratios (see Table 1), and we needed to determine the possible influence of sex on the children's cognitive development. The total number of boys ($n = 17$) in the control group was compared with the total number of girls ($n = 34$) in the control group using the Mann-Whitney U test. We found a high possibility of similarity in the neuropsychological parameters in boys and girls (executive function: $U = 189.5$, $p = .263$; verbal performance: $U = 217.5$, $p = .709$; non-verbal performance: $U = 215.0$, $p = .636$; energy level: $U = 232.5$, $p = 1.000$). The absence of an influence of sex allowed us to ignore this factor when comparing the neuropsychological parameters in the main and control groups.

The between-group comparison of neuropsychological scores revealed significantly more pronounced deficits in all of the analyzed cognitive components in children with ADHD symptoms compared with controls in both the 7-8- and 9-10-year-old age groups (Table 3). The mean values of the neuropsychological indices are shown in Figure 2.

We analyzed age-related differences in neuropsychological indices in children with ADHD symptoms and controls (Figure 3, Table 4). Both groups showed progressive age-related changes. The control group exhibited significant age-related changes only in executive function. ADHD children presented an improvement in all cognitive components except energy level. Notably, despite the progressive changes in all of the neuropsychological parameters, ADHD children aged 9-10 years continued struggling with pronounced regulatory deficits and partial verbal and non-verbal impairments (Table 3).

The fact that ADHD children in both age groups had multiple cognitive deficits raises the issue of whether these deficits result from a whole-brain mechanism or reflect heterogeneous impairment caused by different neurophysiological factors. Our

Table 3. Statistical differences in neuropsychological scores between ADHD groups and age-matched controls.

Age	Neuropsychological indices	ADHD (entire group) *vs.* Controls	ADHD FTW *vs.* Controls	ADHD RH *vs.* Controls	ADHD DA *vs.* Controls	ADHD FTW *vs.* RH	ADHD FTW *vs.* DA	ADHD RH *vs.* DA
7-8 years	Executive dysfunctions	U = 164.5 $p < .0001$	U = 41.0 $p < .0001$	U = 42.5 $p = .047$	U = 48.0 $p = .240$	U = 63.0 $p = .022$	U = 43.5 $p = .007$	U = 23.5, $p = .613$
	Verbal impairments	U = 184.5 $p < .0001$	U = 53.5 $p < .0001$	U = 59.0 $p = .304$	U = 43.0 $p = .104$	U = 66.0 $p = .024$	U = 47.0 $p = .011$	U = 26.0 $p = .867$
	Non-verbal impairments	U = 148.5 $p < .0001$	U = 94.0 $p < .0001$	U = 0 $p < .0001$	U = 28.0 $p = .019$	U = 59.5 $p = .012$	U = 111.5 $p = .799$	U = 12.5 $p = .012$
	Low energy level	U = 261.0 $p < .0001$	U = 140.0 $p < .0001$	U = 52.0 $p = .165$	U = 30.0 $p = .026$	U = 104.0 $p = .320$	U = 109.0 $p = .747$	U = 23.0 $p = .613$
9-10 years	Executive dysfunctions	U = 163.5 $p < .0001$	U = 32.0 $p = .027$	U = 0 $p = .001$		U = 61.0 $p = .533$		
	Verbal impairments	U = 317.0 $p < .0001$	U = 35.5 $p = .042$	U = 17.5 $p = .383$		U = 49.0 $p = .208$		
	Non-verbal impairments	U = 294.0 $p < .0001$	U = 39.0 $p = .071$	U = 5.5 $p = .011$		U = 68.5 $p = .796$		
	Low energy level	U = 243.5 $p < .0001$	U = 28.0 $p = .014$	U = 14.0 $p = .209$		U = 55.5 $p = .348$		

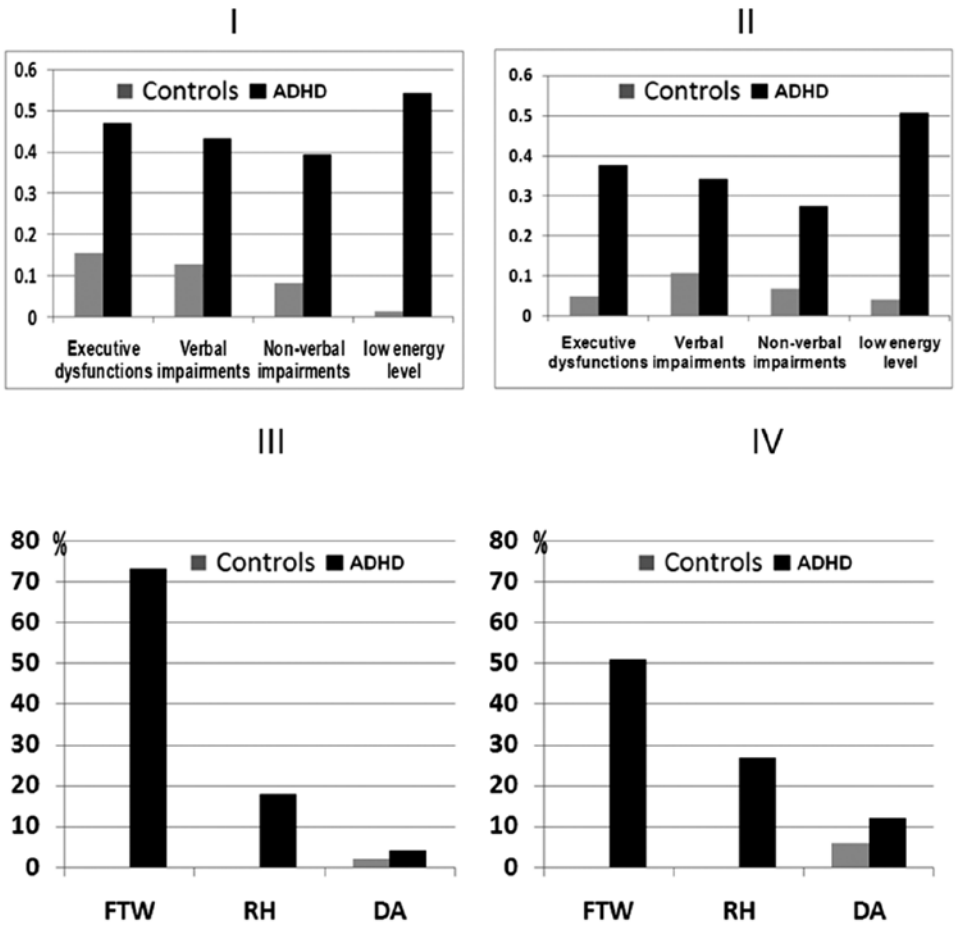

Figure 2: (Upper line) Mean group values of integral neuropsychological indices, showing deficits in different cognitive processes: (1) executive function, (2) verbal performance, (3) non-verbal performance, and (4) energy level in children in the control group (gray columns) and children with ADHD symptoms. (I) Children aged 7-8. (II) Children aged 9-10. (Lower line) Frequency of cases with EEG patterns that reflect non-optimal functioning of the fronto-thalamic system (FTS), local abnormal electrical activity in the right hemisphere (RH), and deficit of cortical activation (DA). Gray columns indicate controls, and black columns indicate children with ADHD symptoms. (III) Children aged 7-8. (IV) Children aged 9-10 years.

previous studies (see Introduction) suggested that the possible neurophysiological factors associated with cognitive deficits in ADHD include fronto-thalamic non-optimal functioning (FTS), a decreased level of cortical excitability (DA), and right hemisphere local deviations (RH; representative EEG patterns are presented in Figure 1). All of these factors can selectively influence different cognitive components alone or in combination.

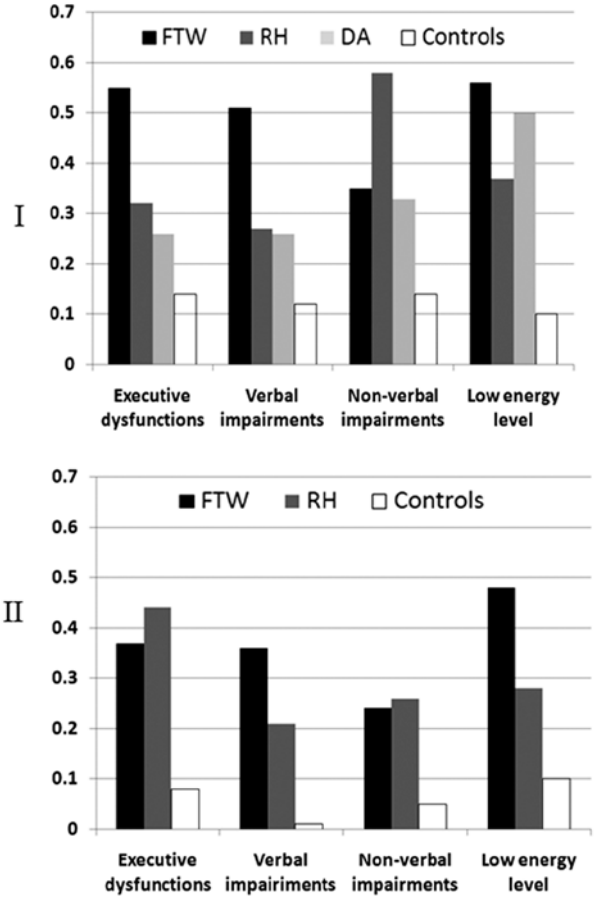

Figure 3. Mean group values of integral neuropsychological indices that show deficits in different cognitive processes. (I) Children aged 7-8. (II) Children aged 9-10.

Specificity of cognitive deficits in ADHD children with different deviating EEG patterns

To study the influence of the potential neurophysiological factors mentioned above on cognitive development in ADHD children, we conducted an interdisciplinary assessment that included two steps. We first recorded a resting-state EEG and checked it for three deviating patterns (illustrated in Figure 1). The deviating patterns should be detected not less than three times during a 3-min recording. ADHD children aged 7-8 differed from their typically developing peers in all three deviating EEG patterns (Figure 2, III). They significantly more often demonstrated fronto-thalamic non-optimal functioning (Pearson $\chi^2_1 = 35.799, p < .0001$) and right hemisphere local deviations (Pearson $\chi^2_1 = 4.554$, $p = .03$) and approached significance in deficits in nonspecific activation (Pearson $\chi^2_1 = 2.758$, $p = .09$). ADHD children aged 9-10 years (Figure 2, IV), like 7-8-year-old children with the same symptoms, significantly more often demonstrated fronto-thalamic non-optimal functioning (Pearson $\chi^2_1 = 13.082$, $p < .0001$) and right hemisphere local deviations (Pearson $\chi^2_1 = 5.244$, $p = .03$) but did not significantly differ from the control group in deficits in nonspecific activation. The latter results possibly reflect the fact that there is an increase in nonspecific activation in children at 9-10 years of age, even in children with ADHD symptoms who earlier exhibited a decrease in cortical activation. The results shown in Figure 2 are consistent with our previous research and provide further confirmation that these brain activity deviations are neurophysiological factors associated with cognitive deficits in ADHD.

According to the individual analysis of resting-state EEG, ADHD children aged 7-8 years and 9-10 years were grouped according to deviating EEG patterns. We formed two sets of three groups: children aged 7-8 years (n = 34) and 9-10 years (n = 21) with EEG patterns of fronto-thalamic non-optimal functioning (FTWs), children aged 7-8 years (n = 8) and 9-10 years (n = 7) with EEG patterns of right hemisphere local deviations (RH), and children aged 7-8 years (n = 7) and 9-10 years (n = 4) with EEG patterns of deficits in nonspecific activation (DA) provided by the brainstem reticular formation. Each subgroup included children with only one type of deviating pattern.

Table 4. Statistical age-dependent differences in neuropsychological scores in the ADHD and control groups.

Neuropsychological Indices	Controls	ADHD (whole group)	ADHD FTW	ADHD RH
Executive dysfunctions	U = 149.5 p = .005	U = 1230.0 p = 0.047	U = 223.0 p = .019	U = 18.5 p = .281
Verbal impairments	U = 206.5 p = .180	U = 1218.5 p = .041	U = 227.0 p = .023	U = 27.0 p = .955
Non-verbal impairments	U = 236.5 p = .485	U = 1128.5 p = .009	U = 268.0 p = .116	U = 5.0 p = .006
Low energy level	U = 217.5 p = .080	U = 1487.0 p = .619	U = 319.0 p = .484	U = 25.0 p = .779

Children with multiple deviating patterns (n = 32) were excluded from further analysis.

In the next step of the study, we compared neuropsychological cognitive activity scores in subgroups of children with different deviating EEG patterns and control groups of the same age. None of the controls aged 7-8 years and 9-10 years had EEG patterns of fronto-thalamic non-optimal functioning or right hemisphere local deviations (Figure 2, III, IV). In the control group, EEG patterns of decreased cortical activation were found only in one case, which was not included in this part of the statistical analysis. We did not perform the statistical analysis of neuropsychological parameters in children with DA aged 9-10 years and their control group because there were only a few cases (n = 4) of this deviating EEG pattern. The comparison of neuropsychological parameters in children with different EEG deviations is shown in Figure 3 and Table 3.

Non-optimal functioning of the fronto-thalamic system was found in the group of younger children (Figure 3, I), which had a statistically significant and pronounced negative effect on all cognitive components that were analyzed, reflected by decreases in neuropsychological indices compared with the control group. Right hemisphere local deviations also negatively affected the children's cognitive performance. The experimental group exhibited significantly more pronounced executive dysfunctions and nonverbal impairments. Children with RH abnormalities exhibited more pronounced nonverbal difficulties than children with FTWs, whereas children with FTWs exhibited significantly more pronounced executive dysfunctions and verbal impairments. Children aged 7-8 years with DA patterns, unlike children with the other two types of abnormalities, did not present any executive dysfunctions. The DA patterns negatively affected the children's energy level (e.g., cognitive processing speed and arousal) and nonverbal performance, although their nonverbal deficits were less pronounced compared with RH children. Thus, 7-8-year-old children with ADHD symptoms presented executive dysfunctions that could be associated with both fronto-thalamic non-optimal functioning and right hemisphere activity local deviations. Verbal impairments were observed only in children with FTWs, whereas nonverbal impairments were observed in all of the groups of ADHD children, with the most pronounced difficulties in the RH group.

Executive function, verbal performance, and cognitive processing speed in children aged 9-10 years, similar to 7-8-year-olds, were negatively influenced by FTWs (Table 3). However, FTWs, which were found in the older group of children, had a more selective influence. Their nonverbal performance was not significantly affected compared with controls. Nonverbal impairments were found only in children with RH deviations. These children also had poor planning abilities. Thus, we found an approximately similar specific influence of deviating brain function on cognitive development in children in both age groups.

Considering the age-dependent improvement in cognitive abilities in ADHD children, we sought to determine whether their cognitive development is influenced by the specificity of brain activity deviations. The results of the statistical analysis of age-dependent changes in the FTW and RH groups are presented in Table 4. The comparison of integral neuropsychological indices in children with FTWs aged 7-8 years and children with FTWs aged 9-10 years revealed a significant improvement in executive function and verbal task performance. The analysis of age-related differences in the groups with RH deviations showed progressive changes in nonverbal function and no significant changes in other neuropsychological indices. Generally, children with ADHD and different types of brain deviating activity exhibited an improvement in cognitive function as they got older. However, the RH children presented age-related improvement only in nonverbal performance and continued to struggle with executive dysfunction during the next stage of development.

Thus, the neuropsychological analysis of cognitive function in ADHD children with different types of deviating brain activity allowed us to determine two neurophysiological factors that significantly impede executive function at both 7-8 years and 9-10 years of age: fronto-thalamic dysfunction and right hemisphere local brain activity deviations. Both patterns were associated with information processing impairment, but both had a specific influence. Fronto-thalamic dysfunction appeared to mainly affect verbal performance, whereas right hemisphere abnormalities appeared to involve deficits in nonverbal functions. A third pattern, a decreased level of cortical activation, was mainly associated with slow processing speed and poor arousal. Children with DA aged 7-8 years also exhibited poor nonverbal information processing. ADHD children aged 9-10 years are very seldom diagnosed with the DA pattern; hence, decreased cortical activation could not be associated with ADHD in this age group.

Discussion

The analysis of neuropsychological parameters revealed less effective executive function in all of the ADHD children compared with typically developing children. These results are consistent with other notions of cognitive deficits in ADHD (Barkley, 2006; Wahlstedt, 2009; Willcutt et al., 2005, Zavadenko & Petroukhin, 2007). The comparison of the results of the neuropsychological and electrophysiological assessments in the present study demonstrated the degree of involvement of neurophysiological factors in executive deficits in ADHD.

ADHD children aged 7-8 years and 9-10 years presented executive dysfunction mainly in cases of FTW patterns in their EEG recordings. The possible immaturity or dysfunction of the fronto-thalamic system in ADHD children was confirmed by

neuromorphological data. Longitudinal studies reported more prolonged maturation of the frontal cortex (Shaw, 2007; Batty, 2010) and cortico-striato-thalamo-cortical network (Stanley et al., 2008) in ADHD compared with typical development.

The possible mechanism that underlies the influence of FTWs on executive function may be related to a deficit of the selective modulation of cortical activity when the brain prepares to perceive and retain relevant information. The involvement of prefrontal cortical and thalamic neurons in the process of the selective modulation of sensory and association cortices was shown in animal neurophysiological studies (for review, see Machinskaya, 2003, Introduction) and confirmed in modern fMRI studies of cognitive brain mechanisms in humans (Watanabe & Funahashi, 2012).

The non-optimal functioning of anterior right hemisphere areas may be another possible neurophysiological factor associated with executive function deficits in ADHD. This possibility is supported by the neuropsychological assessment of cognitive functions in children with right hemisphere local EEG deviations who exhibited a significant increase in executive function deficits compared with the control group. Our previous neuropsychological study of 7-10-year-old children with right hemisphere local EEG deviations (Semenova & Machinskaya, 2011) showed that subjects mostly suffered from poor planning and had difficulty staying focused on a task. In the present study, we found no local deviations of right hemisphere activity among the controls, whereas the group with behavioral symptoms of ADHD was diagnosed with this EEG pattern in a large number of cases. The presence of RH patterns in ADHD children is consistent with the RH structural specificity in this syndrome (i.e., a reduction of gray matter volume in the frontal and parietal cortices and paleostriatum compared with controls; McAlonan et al., 2007). Most of the children who were included in the group with RH patterns (12 of 15) had this deviating brain electrical activity located in the frontal and/or inferior temporal cortices. Right hemisphere anterior areas are associated with sustained attention and executive control that are involved in relevant information processing during conflict tasks (Posner & Petersen, 1990) and maintaining sensory-specific cortex activity when retaining information in working memory (Machinskaya & Kurgansky, 2012). Deviating EEG patterns that were recorded from the right hemisphere in children with ADHD symptoms reflect the non-optimal functioning of right hemisphere anterior areas in the resting state; hence, these structures cannot appropriately maintain executive function and selective attention.

When designing this study, we assumed that a variety of partial cognitive deficits in ADHD are caused by different neurophysiological factors. The comparison of neuropsychological scores in children with different functional deviations in the brain confirmed this assumption. We found that 7-8- and 9-10-year-old children with EEG patterns of fronto-thalamic non-optimal functioning exhibited poor verbal performance and pronounced executive function deficits. Our previous studies showed that children aged 7-8 years with FTW patterns mainly suffered from poor semantic processing, reflected by the substitution of semantically related but incorrect words when retelling a text, writing dictation, and performing visuospatial tasks (i.e., recognizing and describing objects; Machinskaya & Semenova, 2004). According to Luria's clinical studies (Luria, 1973), the nominative function of speech is provided by left hemisphere structures and disturbed in cases of left hemisphere frontal and temporal lesions. It was precisely these areas that showed decreased cortico-cortical connectivity in children with fronto-thalamic dysfunction in an EEG coherence study (Machinskaya & Kurgansky, 2013). By comparing the results of electrophysiological and neuropsychological studies of syndromes associated with local brain lesions, we can assume that poor semantic performance in FTW children may result from a decrease in the functional interaction between frontal and temporal left hemisphere cortices.

Groups of children with RH patterns aged 7-8 years and 9-10 years presented the most pronounced nonverbal difficulties compared with typically developing controls and FTW peers. A more detailed neuropsychological assessment of 7-10-year-old children with RH patterns (Semenova & Machinskaya, 2011) showed pronounced deficits of visual perception and visual memory and poor praxis of left hand tactile perception. These observations agree with neuropsychological data on patients with right hemisphere lesions who have poor visuoconstructive abilities, difficulties in visuospatial processing, poor somatognosis, and poor visual memory (Lezak, 1995; Kolk & Talvik, 2002).

Thus, two of three deviating EEG patterns that were detected in children with ADHD symptoms aged 7-8 years and 9-10 years were associated with pronounced partial cognitive deficits, which depended on the type of brain activity deviations.

The low level of cortical excitability found mainly in the younger ADHD group was reflected by a low energy level and slowness but did not impede executive function or verbal performance. In addition to a low energy level, children aged 7-8 years exhibited non-verbal impairments, although these impairments were less pronounced compared with children with RH patterns. Poor non-verbal (visual and somatosensory) processing in children with DA patterns may be caused by the non-optimal function of the occipital and parietal cortices, reflected by hypersynchronous alpha or slow-wave activity in caudal areas.

The comparison of neuropsychological parameters in EEG-homogeneous groups of 7-8- and 9-10-year-old children revealed the age-related specificity of cognitive processes. Typically developing 9-10-year-olds presented progressive changes mainly in executive function. Such improvements are caused by frontal cortex development in children from 7-8 to 9-10 years

of age and the increasing involvement of the frontal cortex in cortical top-down modulation during cognitive performance (Farber & Njiokiktjien, 1993).

Children aged 9-10 years with FTW patterns, similar to controls, exhibited significant improvement in executive function. These positive changes in FTW children aged 9-10 years could be caused by cortex maturation, reflected by an increase in the relative power of the resting-state alpha rhythm (Sokolova & Machinskaya, 2006). Morpho-functional maturation of the cortex may allow its differential involvement in cognitive processing and more effective selective activation of the cortices (Machinskaya, 2006). Together with improvements in executive function, ADHD children aged 9-10 years exhibited significant improvement in verbal performance, which is consistent with an increase in cortico-cortical functional connectivity between frontal and temporal left hemisphere areas (Machinskaya & Kurgansky, 2013).

Children with RH patterns aged 9-10 years showed progressive improvements in only non-verbal performance compared with the 7-8-year-olds, whereas no progressive changes in executive function were found. The pronounced deficit in executive function in 9-10-year-old children with RH patterns suggests less possible compensation of brain morpho-functional maturation compared with FTW deviations.

We found no DA patterns in the older group of children, thus making it impossible to analyze cognitive changes in children with this EEG pattern from 7-8- to 9-10 years of age. However, the absence of DA cases among the older children suggests a possible age-related increase in nonspecific activation and a reduction of DA-dependent cognitive and behavioral difficulties. This agrees with ADHD data collected from different age groups (Weiss & Trockenberg Hechtman, 1993). Adults and adolescents exhibit less pronounced hyperactivity (Matousek et al., 1984; Barry et al, 2003) that appears to be specific for preschool and primary school children with DA.

Conclusions

The neuropsychological assessment of cognitive abilities in 7-8- and 9-10-year-old children showed executive function deficits and verbal and non-verbal impairments in cases with ADHD symptoms compared with typically developing peers. Children with ADHD symptoms aged 7-8 years and 9-10 years significantly more often exhibited EEG patterns of fronto-thalamic non-optimal functioning and right hemisphere local deviations of brain electrical activity compared with controls. In addition to these deviations, the younger group showed EEG patterns that reflected brain activation deficits. Executive dysfunctions were found in children in both age groups with EEG patterns of fronto-thalamic non-optimal functioning and right hemisphere local deviations of brain electrical activity. A variety of cognitive deficits that were found in children with ADHD symptoms may be explained by functional brain specificity in which fronto-thalamic dysfunction mainly affects verbal performance, and right hemisphere abnormalities mainly involve nonverbal impairments. The comparison of neuropsychological parameters in EEG-homogeneous groups of children aged 7-8 years and 9-10 years showed the following age-related specificity:

- Typically developing 9-10-year-old children exhibited progressive cognitive changes mainly in executive function.
- Children aged 9-10 years with EEG patterns of fronto-thalamic dysfunction exhibited significant improvement in executive function and verbal performance, but there was still a gap between them and their typically developing peers.
- Children aged 9-10 years with EEG patterns of right hemisphere local deviations exhibited positive changes in non-verbal performance compared with 7-8-year-olds but continued to struggle with executive dysfunctions.

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